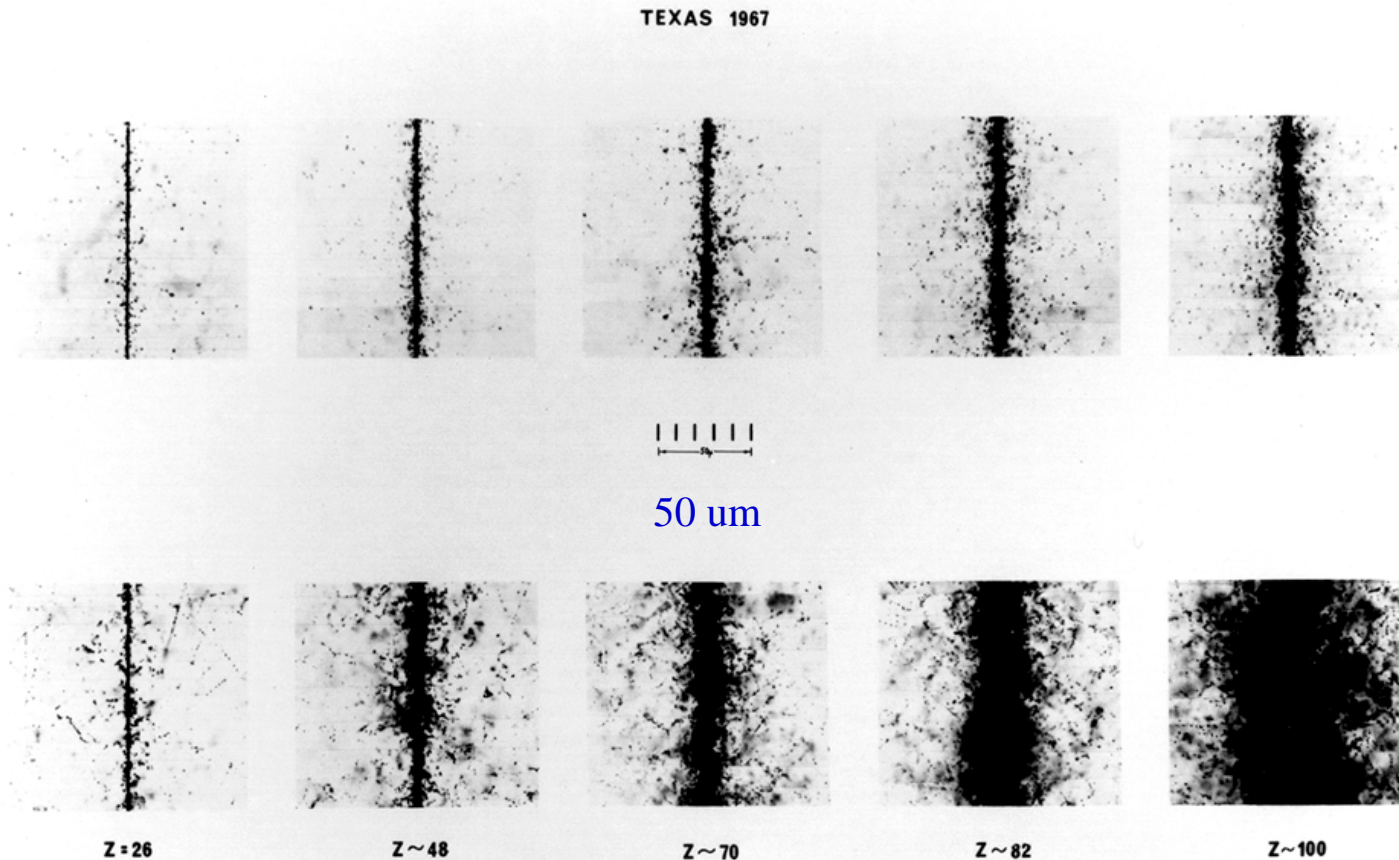


A Brief Review of Charged Particle Radiobiology

Gregory Nelson, Ph.D.

Loma Linda University Radiobiology Program
Department of Radiation Medicine

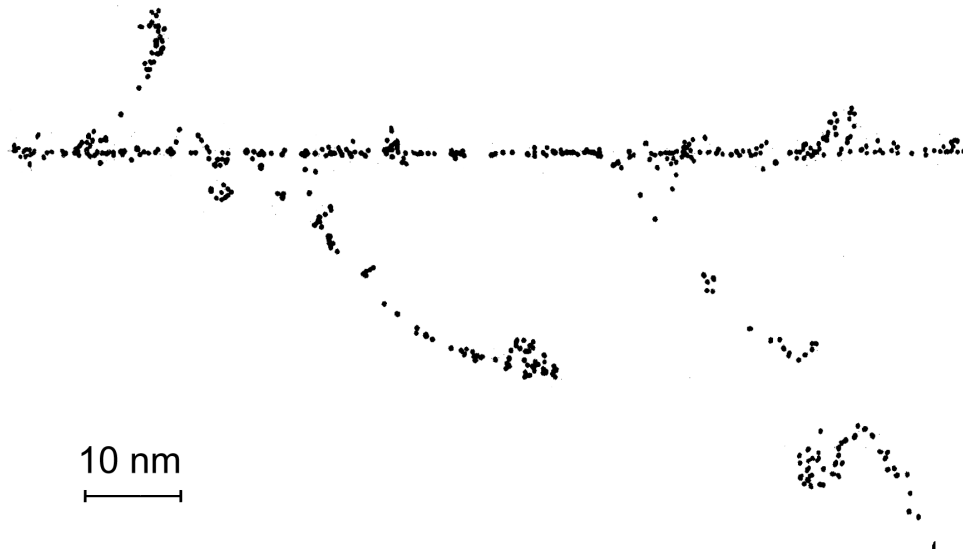
The Appearance of Cosmic Ray Tracks in Nuclear Emulsions



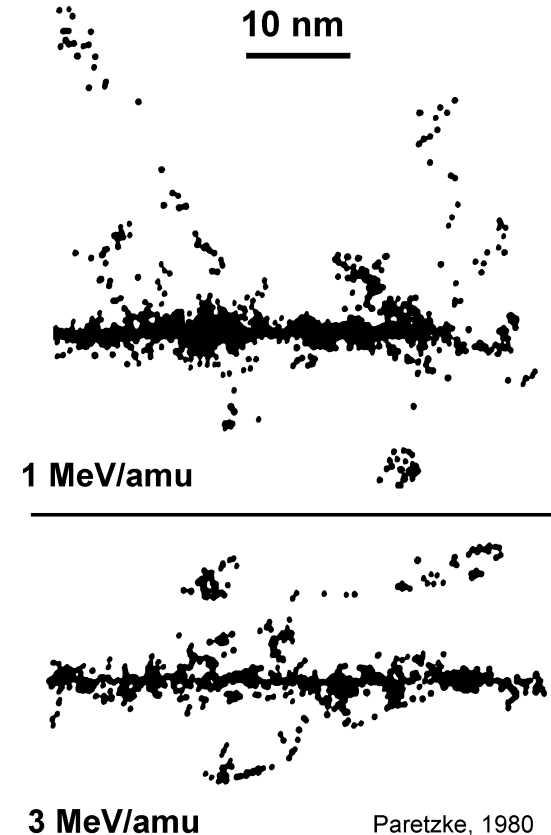
EXAMPLES OF TRACKS OF FIVE RELATIVISTIC COSMIC RAY PRIMARIES. EACH TRACK IS SHOWN IN G.2 AND G.5 EMULSION.

Monte Carlo Simulation of Tracks

8 MeV alpha Particle Track Segment. Goodhead (1989)

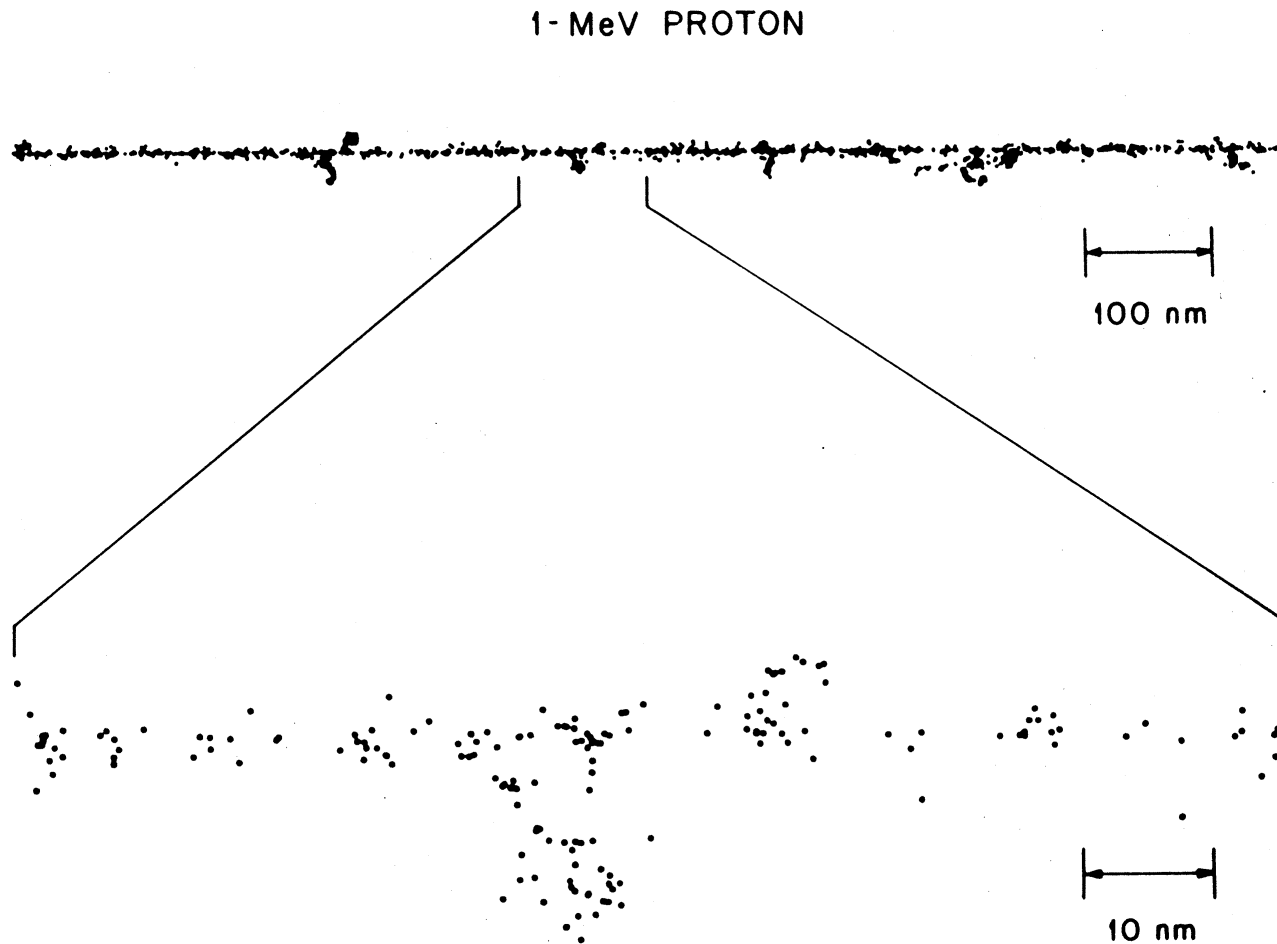


Carbon Ion Tracks

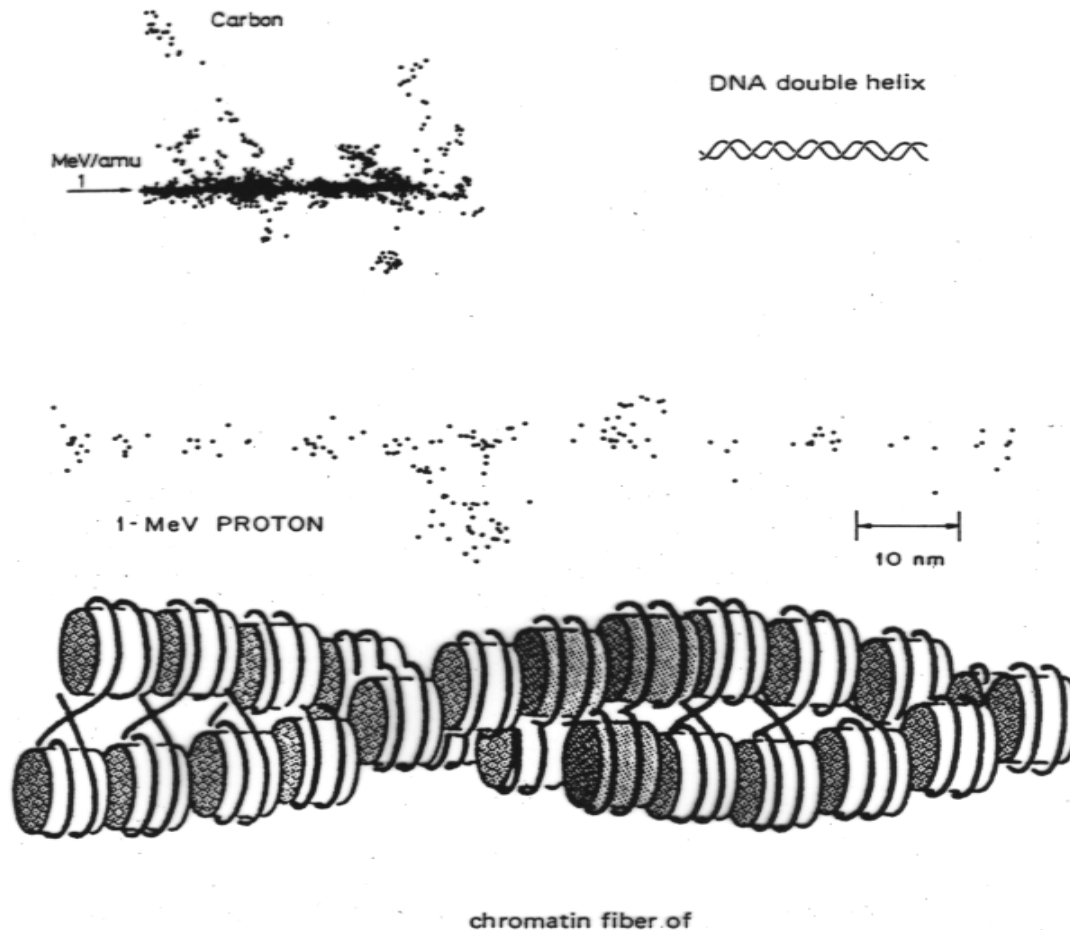


Low Energy Alpha Particle and
Carbon Ions at Two Energies

Simulated Proton Track



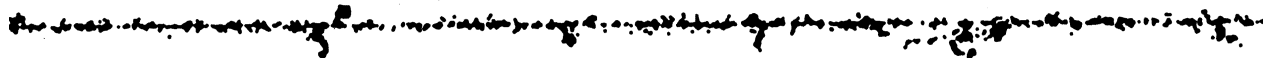
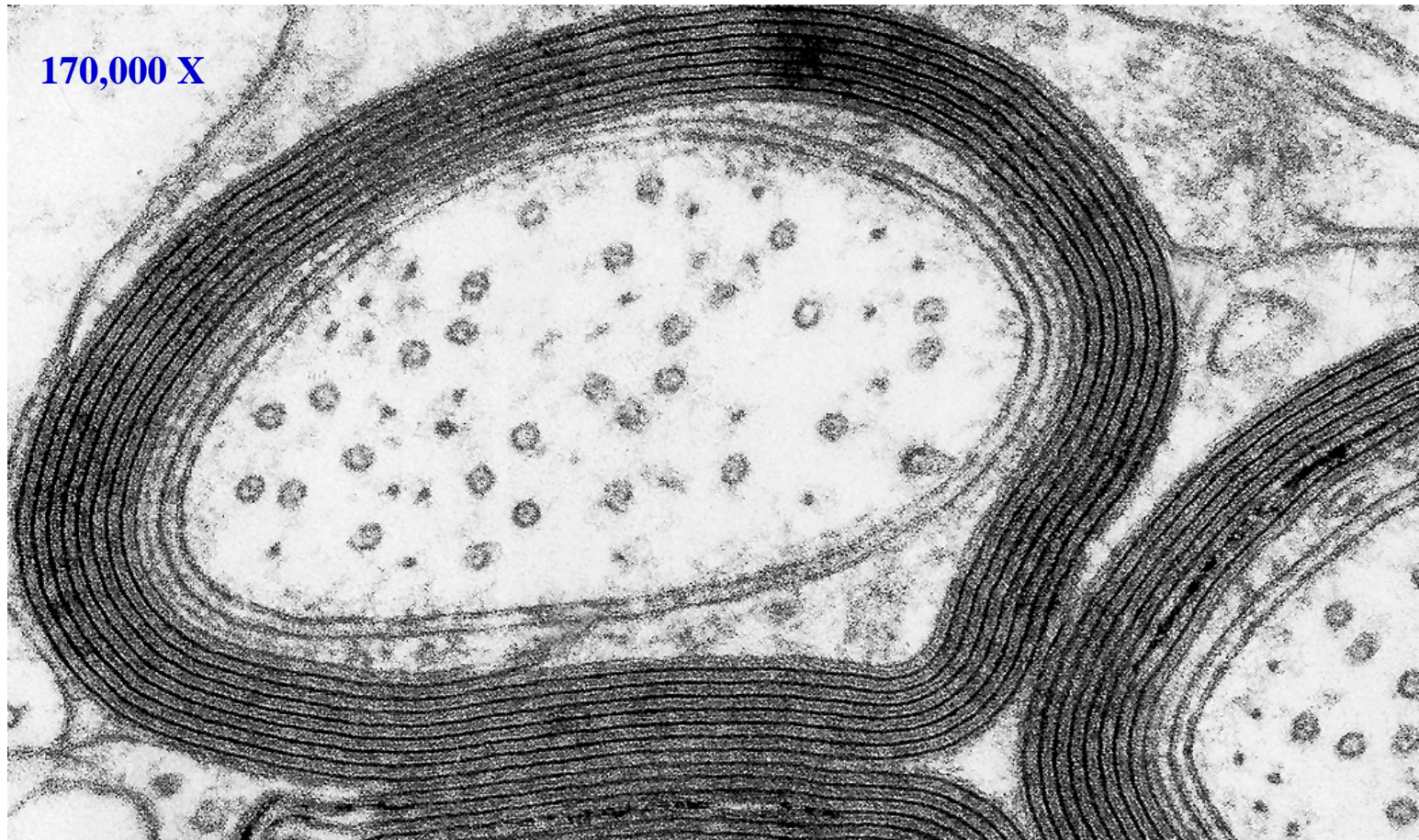
Particle Tracks Place Clusters of Ionizations in Volumes on the Scale of Chromatin



Myelinated Nerves

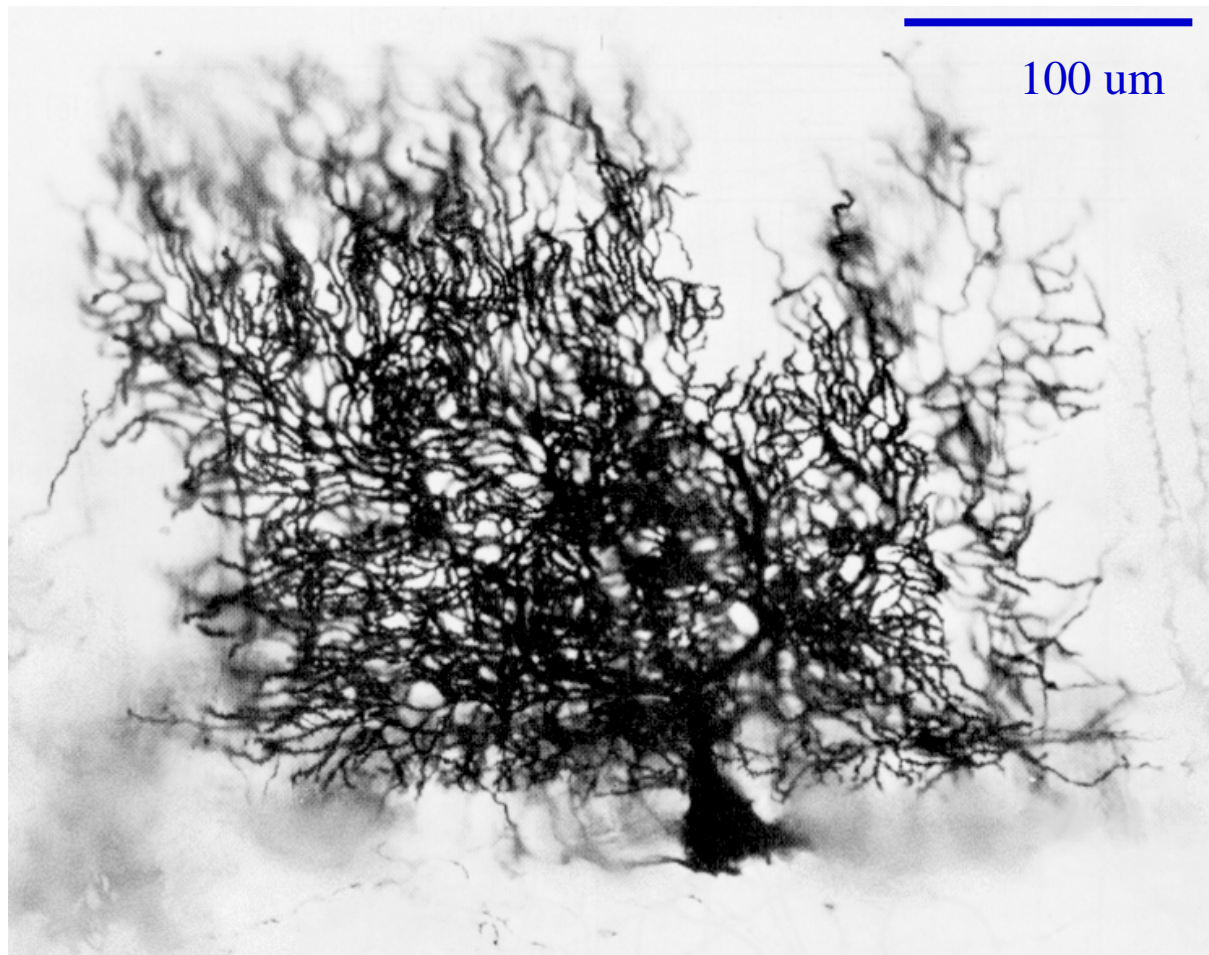
Adult Rat Optic Nerve

Peters et al. (1991) The Fine Structure of the Nervous System. Fig. 6-9

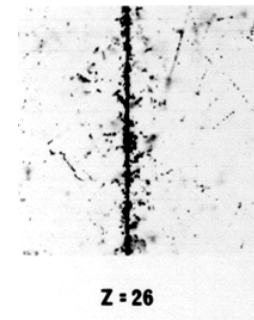


1 MeV Proton

Purkinje Cell

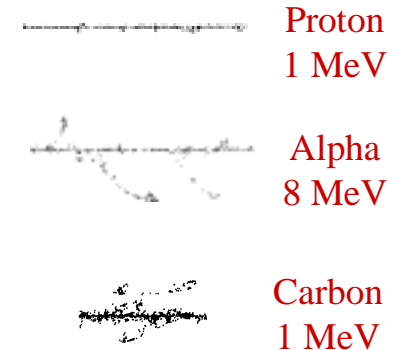
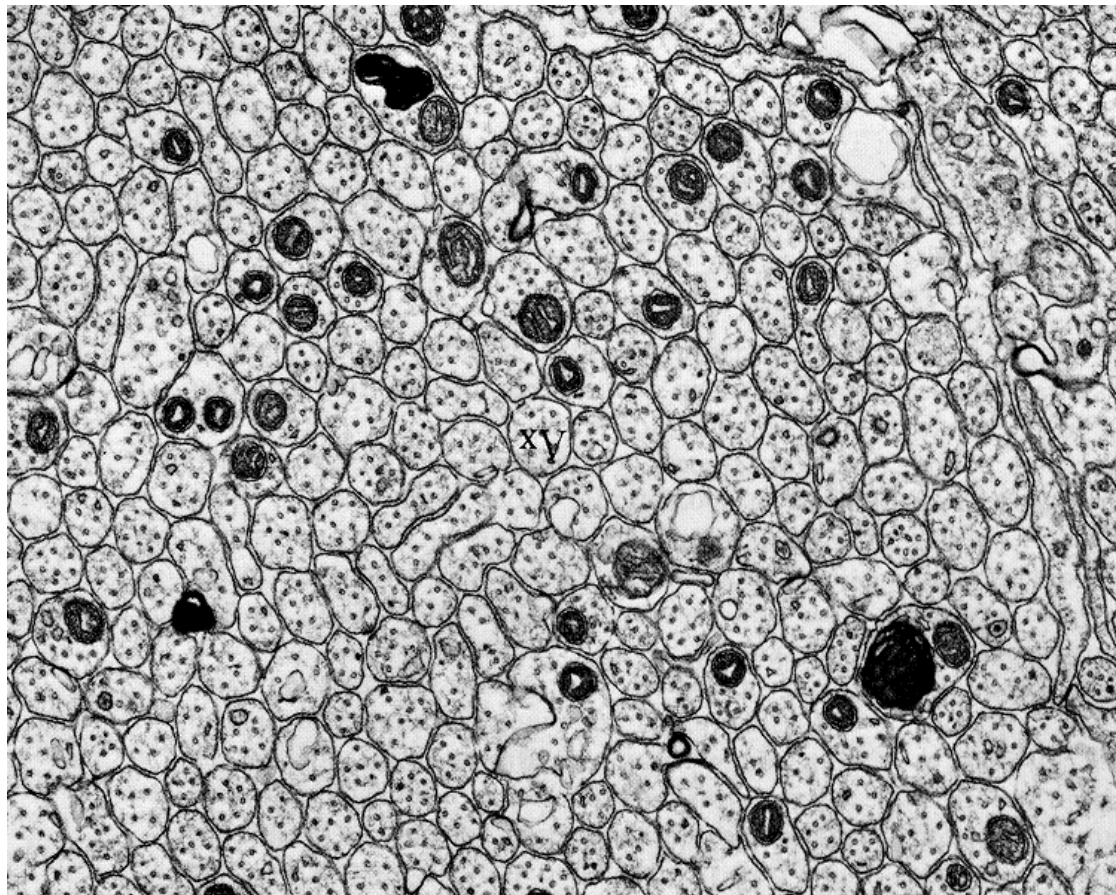


Segment of
Iron Ion
Track in
Nuclear
Emulsion



Axon Bundle in Olfactory Nerve

Rhesus Monkey

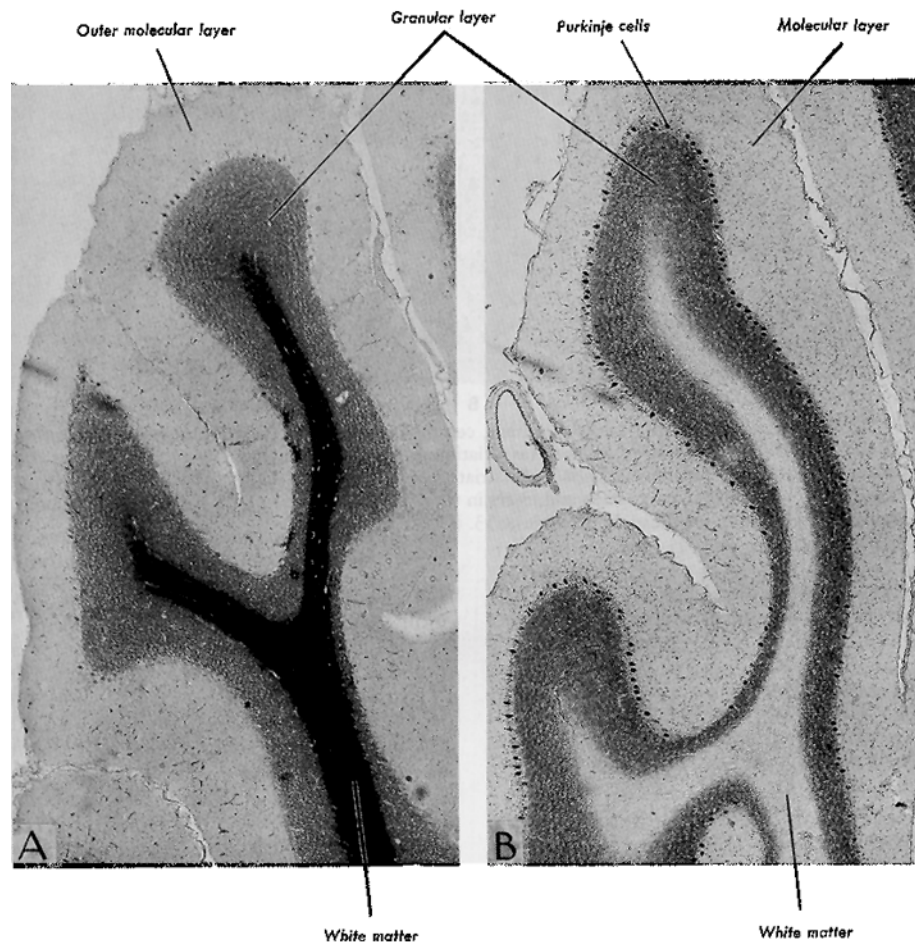


100 nm

29,237X
1 cm = 34 nm

Peters et al. (1991) The Fine Structure of the Nervous System. Fig. 4-15

Human Cerebellum Structure



Weigert-Weil method (A) shows myelinated fibers. Thionine (B) stains cells.

*From Bloom & Fawcett
Textbook of Histology.*

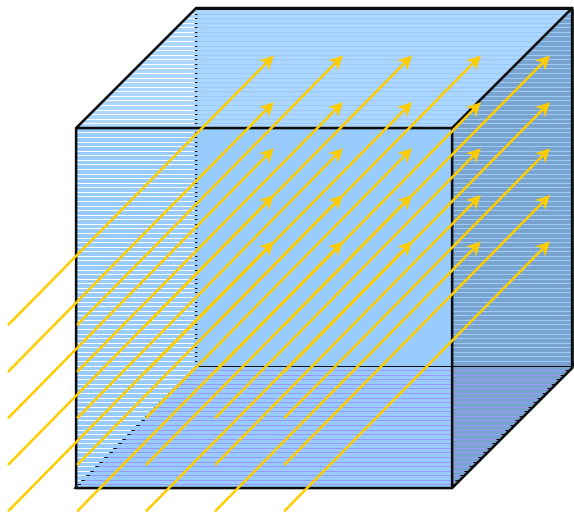


Iron Ion Track Segment

The Fundamental Concept of Dose Can Be Fallacious

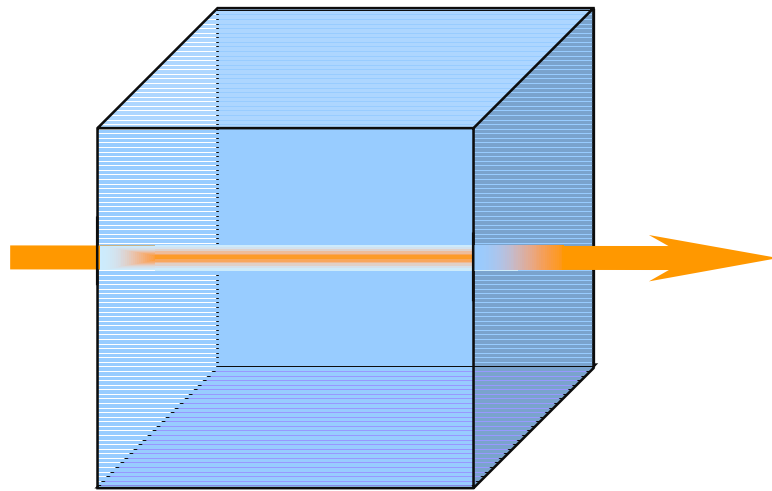
- ◆ Dose is defined as energy absorbed per unit mass
(irrespective of the spatial distribution of the absorbed energy)

1 Dose Unit



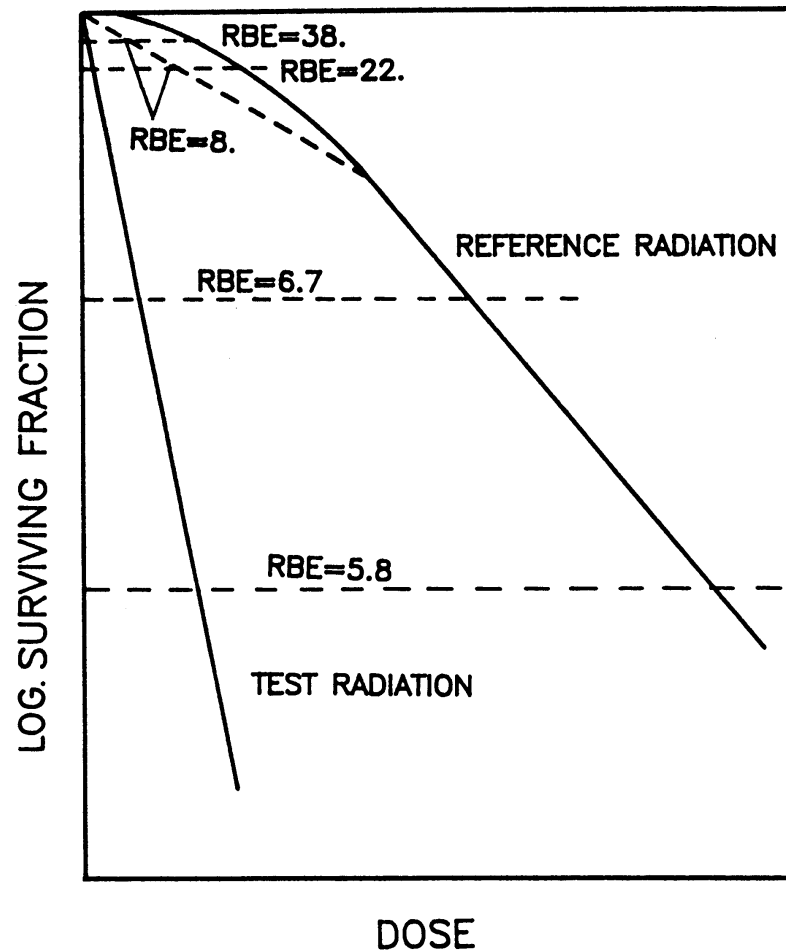
**Low LET radiation deposits
energy in a uniform pattern**

1 Dose Unit



**High LET radiation deposits
energy in a non-uniform pattern**

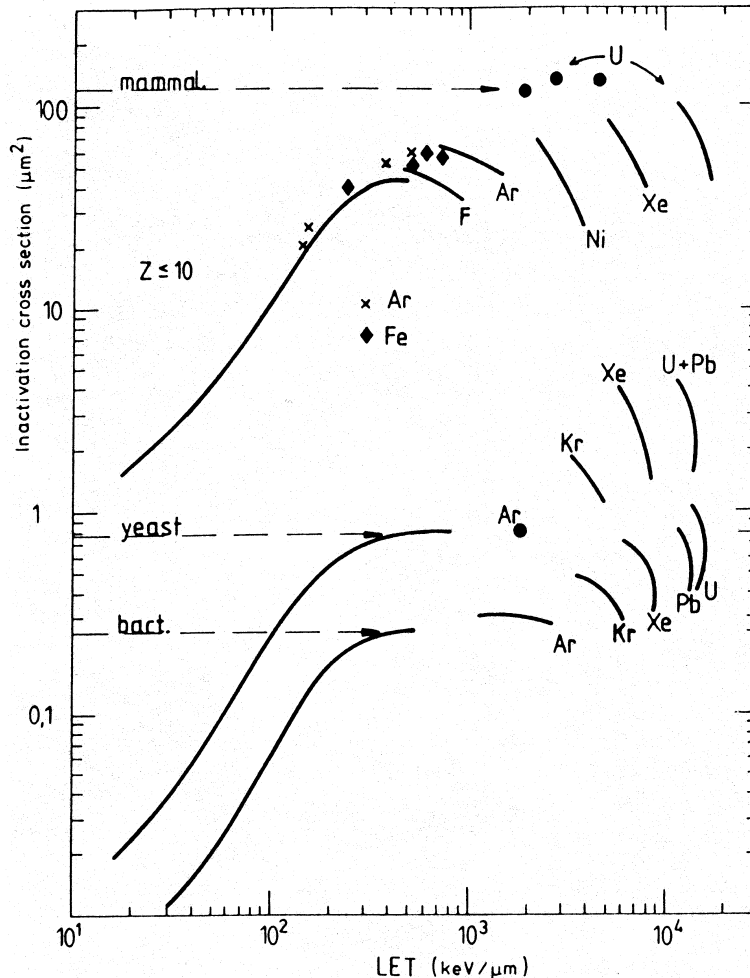
Relative Biological Effectiveness



RBE is used to compare different “qualities” of radiation.

J. Kiefer (1990)

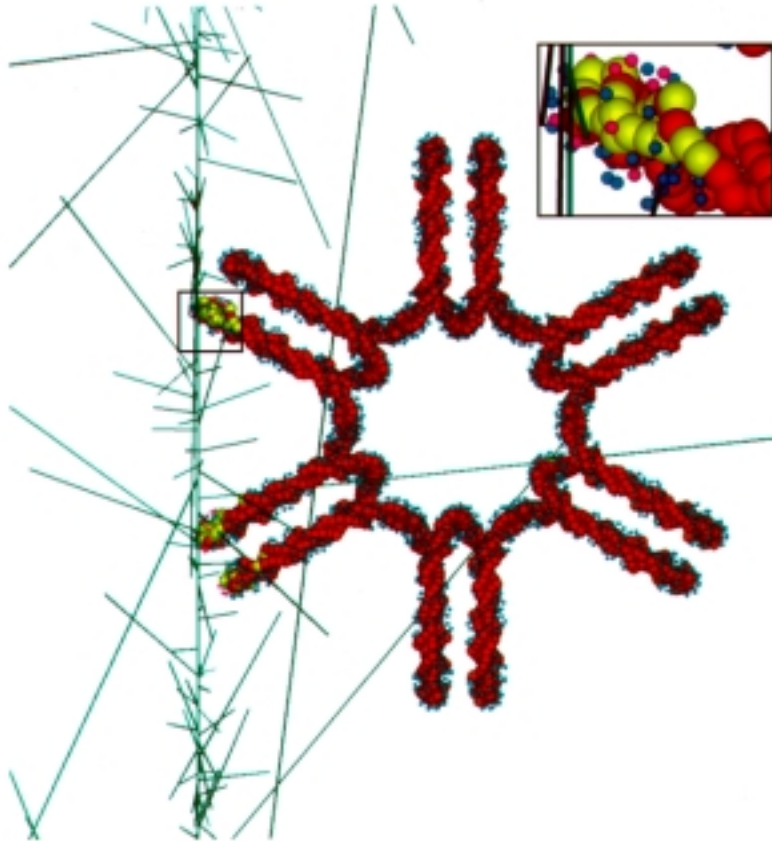
Cross Section vs LET for Cell Inactivation



LET is not uniquely determined so the c.s. vs LET relation is not a function

J. Kiefer (1990)

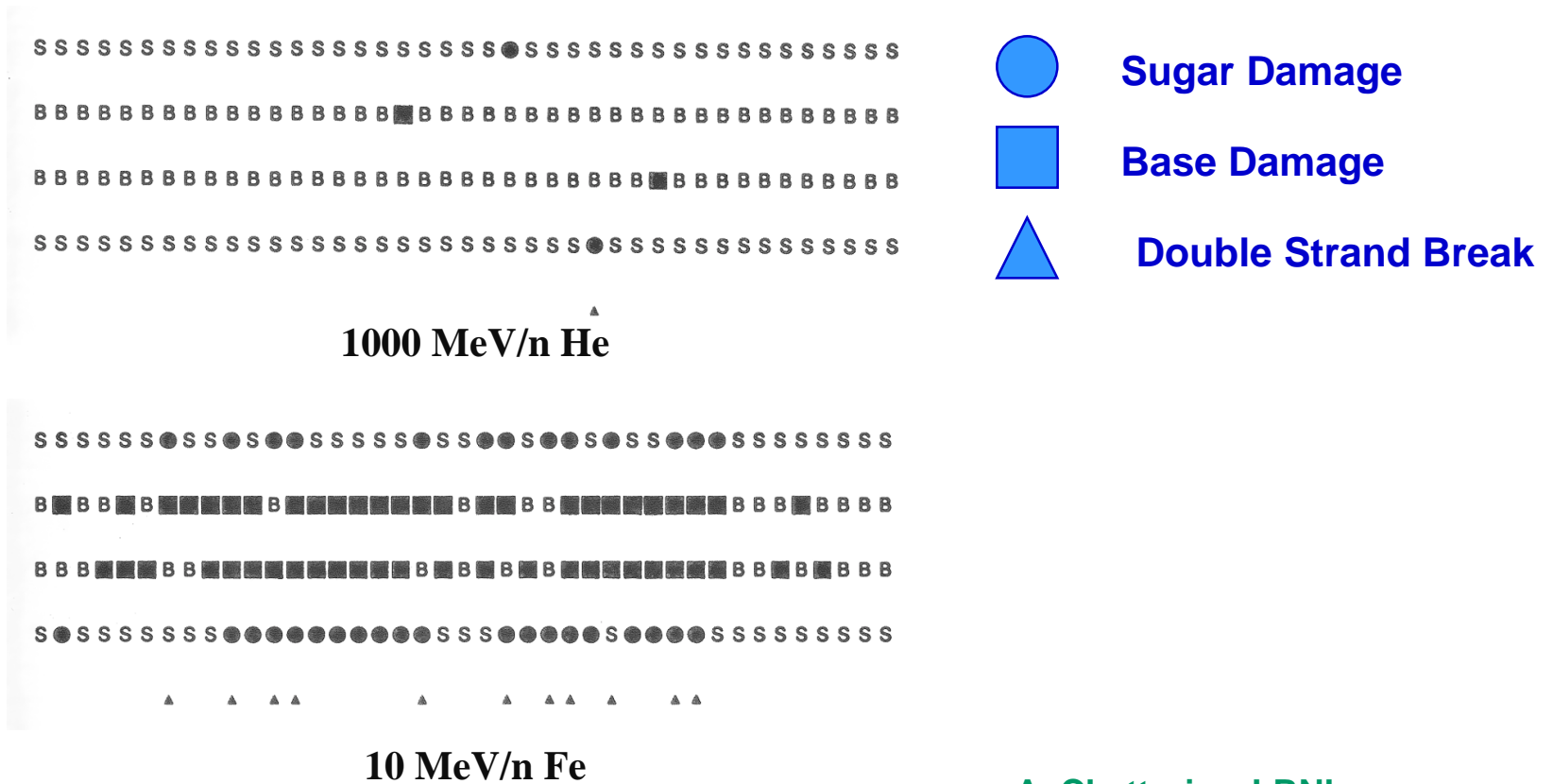
Correlated Damage



- ◆ **The organization of chromatin favors the production of multiple damage sites within loops and nucleosomes.**
- ◆ **Such patterns are unique to charged particle radiation.**

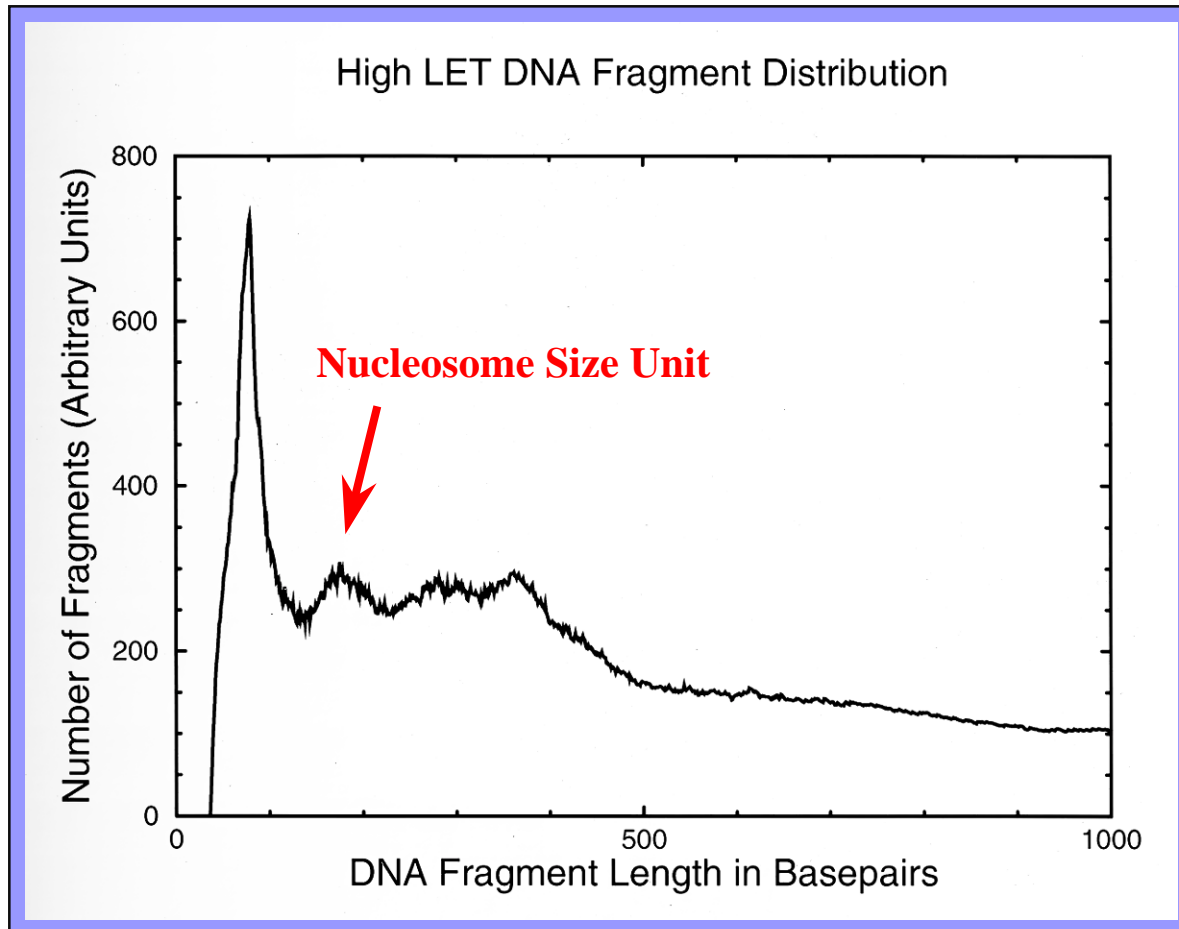
A. Chatterjee, LBNL

Damage Clusters in DNA



A. Chatterjee, LBNL

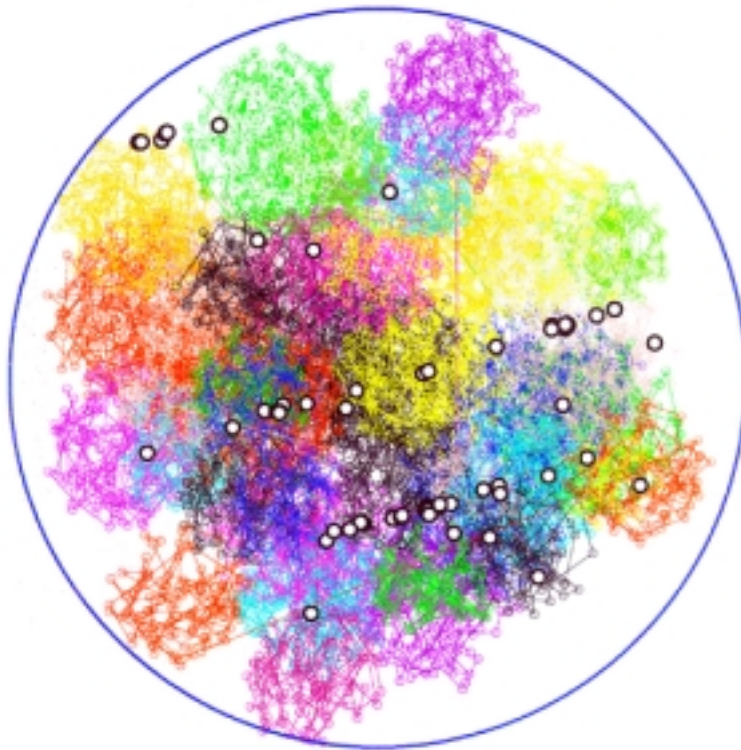
Charged Particles Fragment DNA in Structure-Determined Length Distributions



Rydberg

Correlated Damage

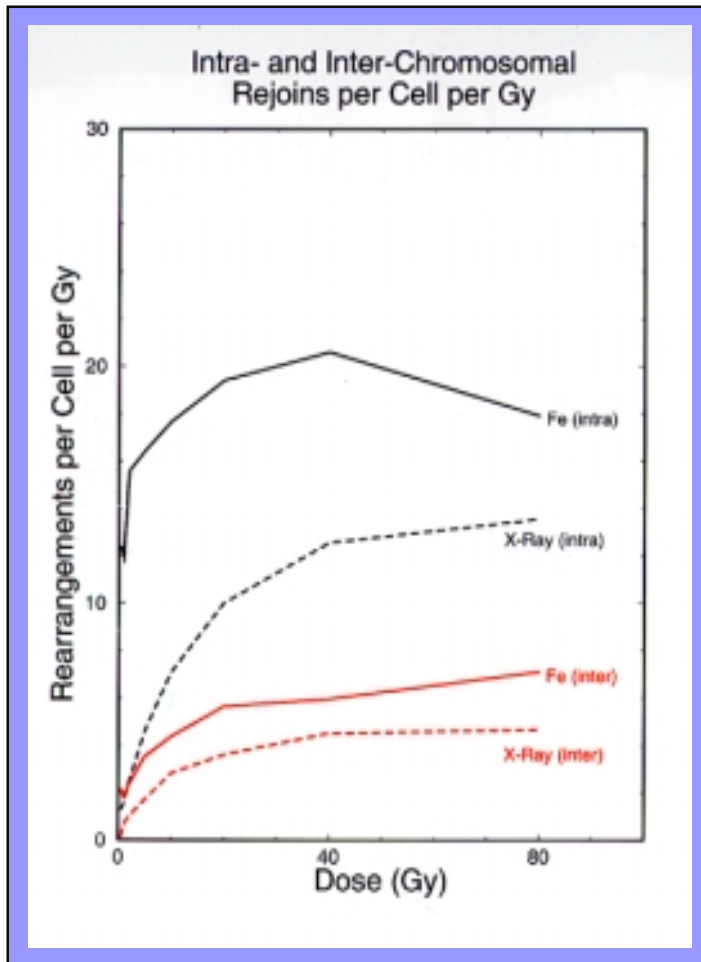
1000 MeV/n Fe Dose=1.0 Gy 81 DSBs
Spherical Nucleus 46 Interphase Chromosomes



- ◆ **Interphase chromatin territories provide a higher order organization favoring spatially correlated damage.**

A. Chatterjee, LBNL

Unique Damage Patterns



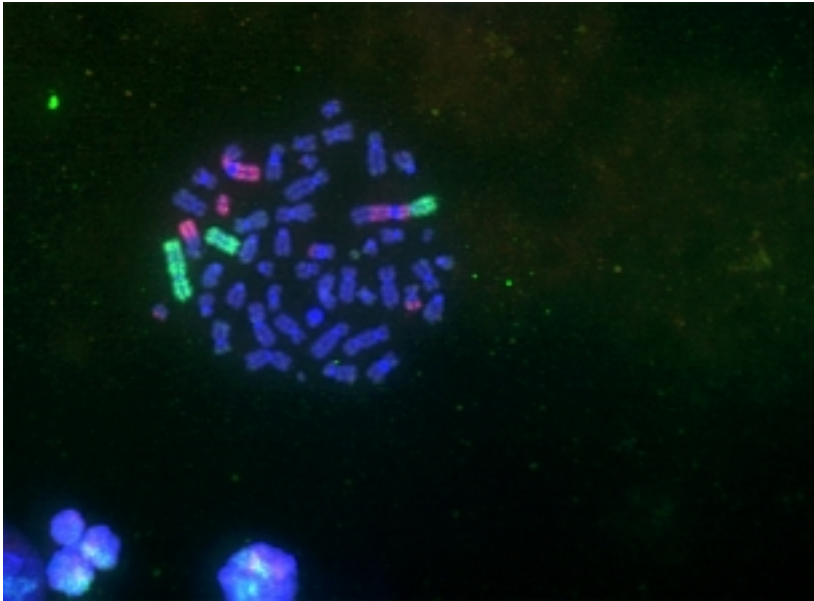
- ◆ A new discovery is the favored production of intra-chromosomal rearrangements by high LET particles

A. Chatterjee, LBNL

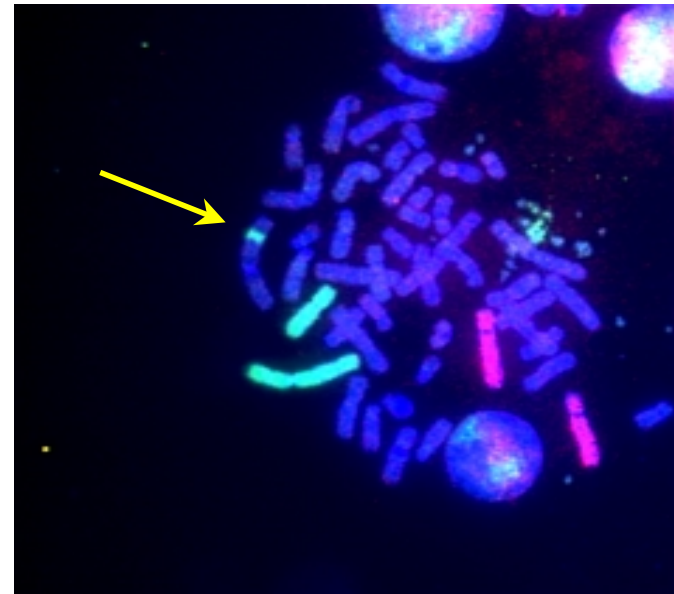
High LET Particles

Generate Complex Chromosome Breaks

BNL 1 GeV Iron Beam

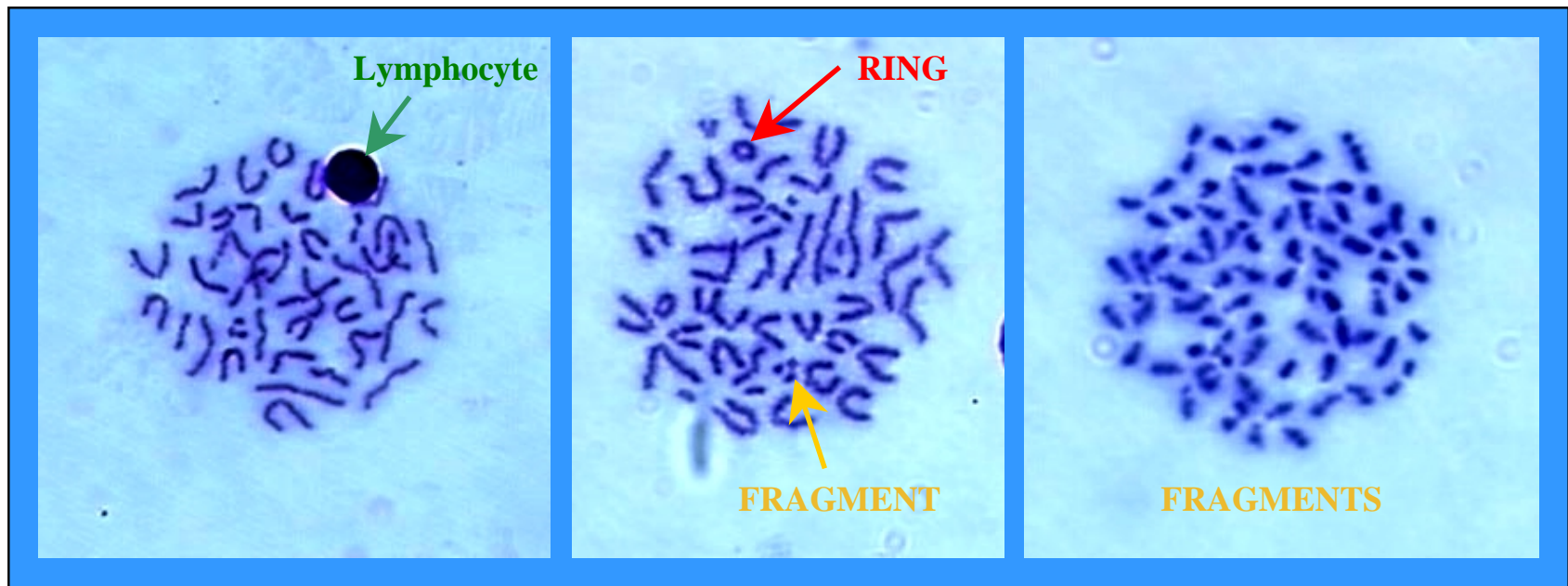


Mir Post-flight Biodosimetry



Chromosome Damage from Proton Exposure

Appearance of Mouse Bone Marrow Cells 24 Hours after Exposure to Protons

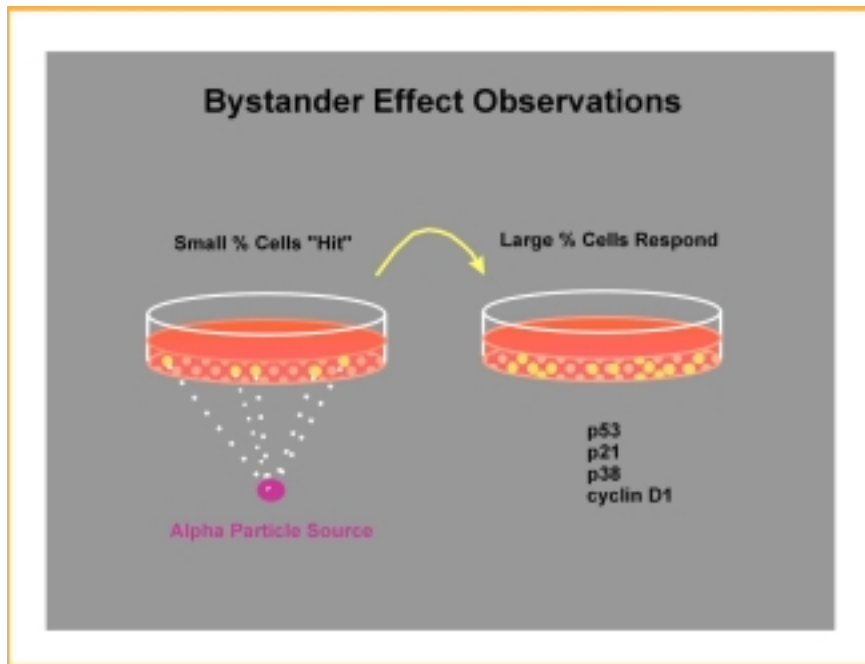


Control

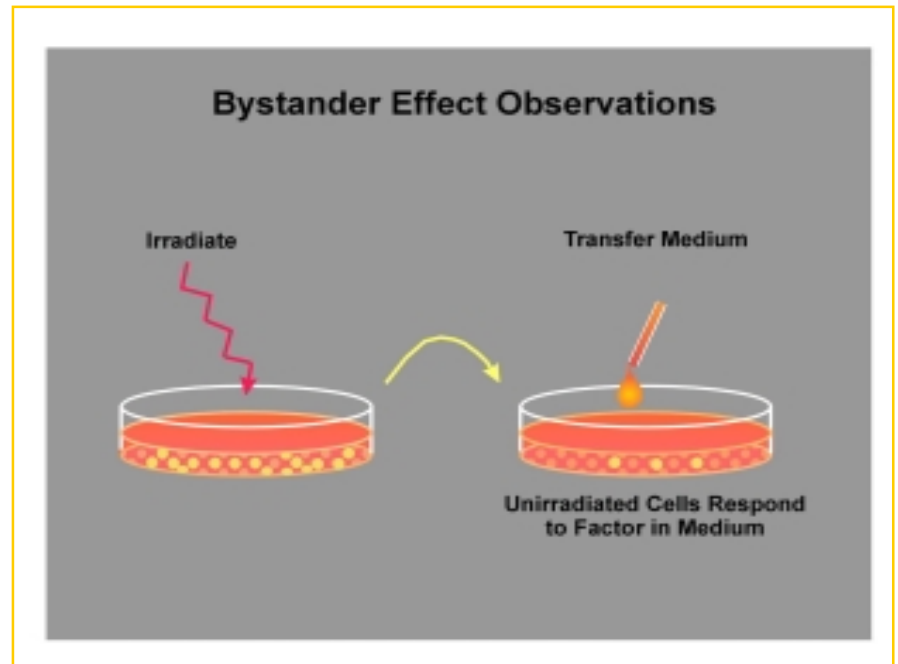
**3 Gray 250
MeV p+**

**3 Gray 250 MeV p+
behind 15 g/cm² Al**

The Bystander Effect



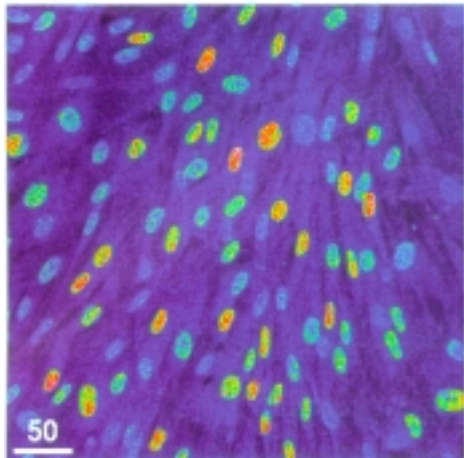
Too Many Cells Respond



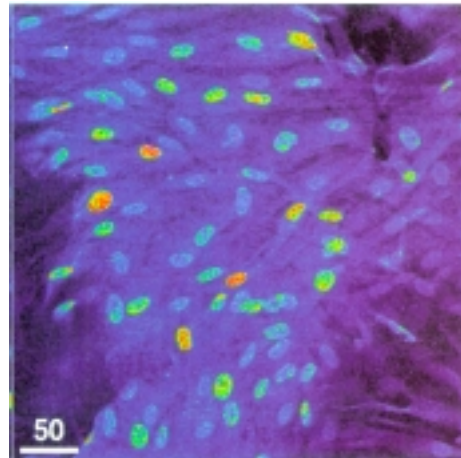
Soluble Factors Implicated

The Bystander Effect

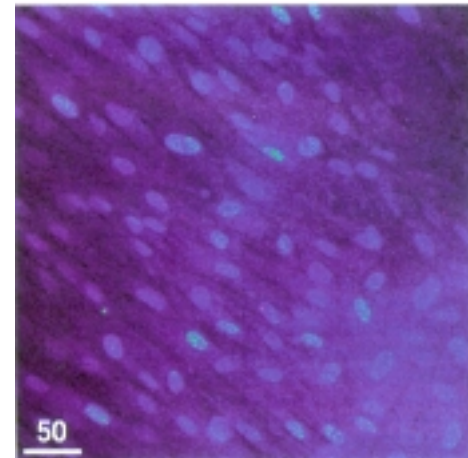
- ◆ **Alpha Particle-Irradiated Human diploid Fibroblasts**
Stained for CDKN1A (p21^{Waf1})



10 cGy



3 cGy - Field 1

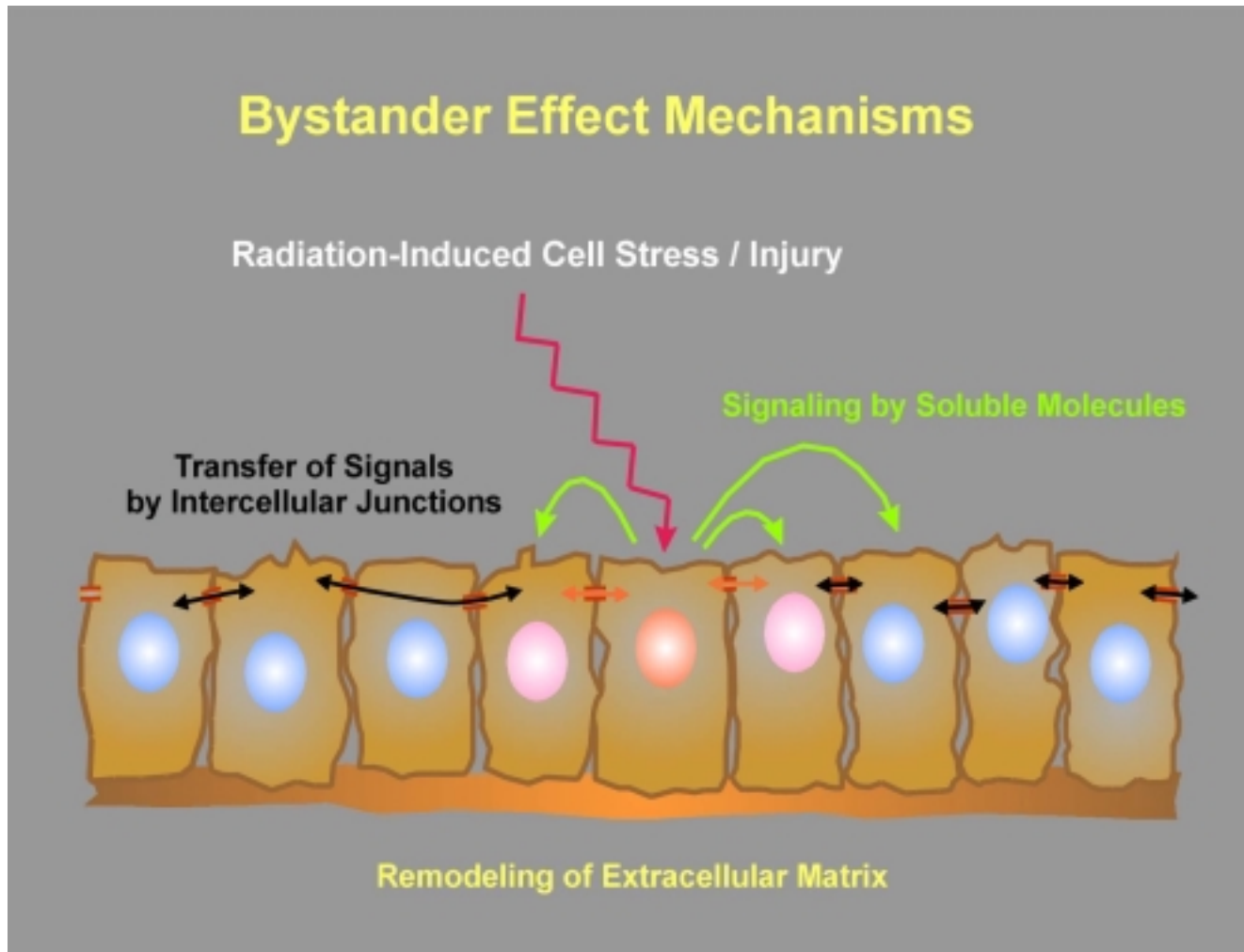


3 cGy - Field 2

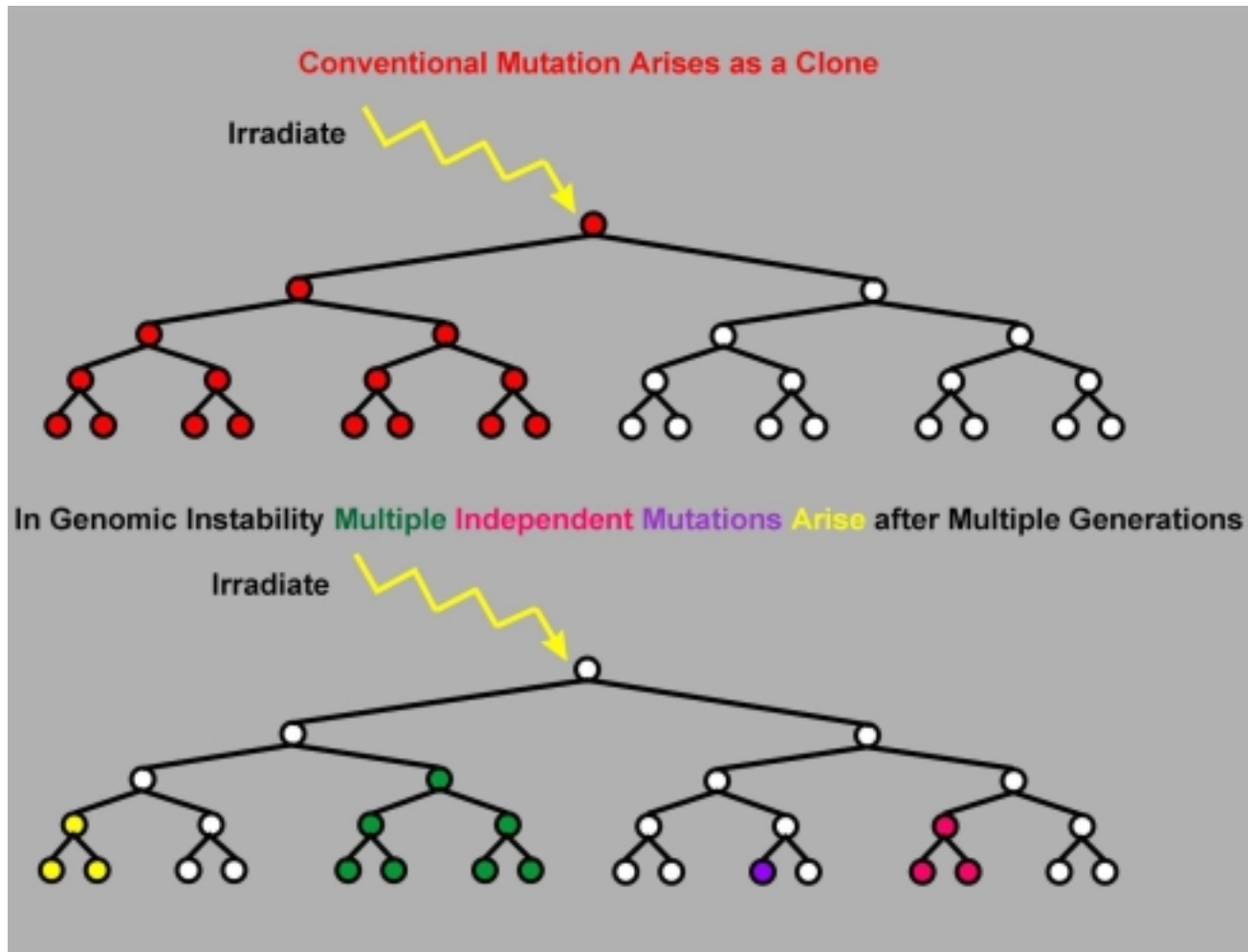
At 10cGy 77% of cells are traversed by an alpha.
At 3 cGy 23% of cells are traversed by an alpha.

Azzam et al. (1998)
Rad. Res. 150: 497.

The Bystander Effect



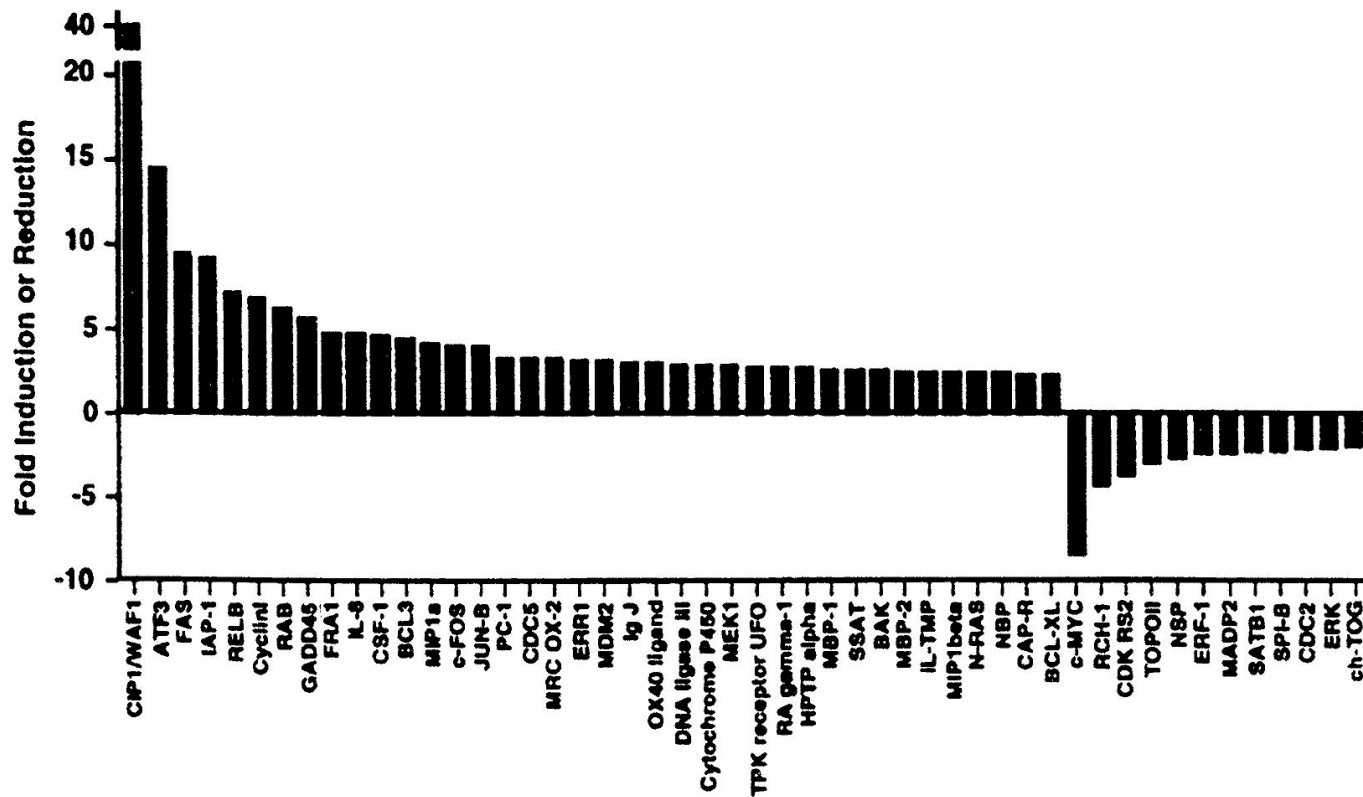
Genomic Instability



Microarray Analysis of ML-1 Cells

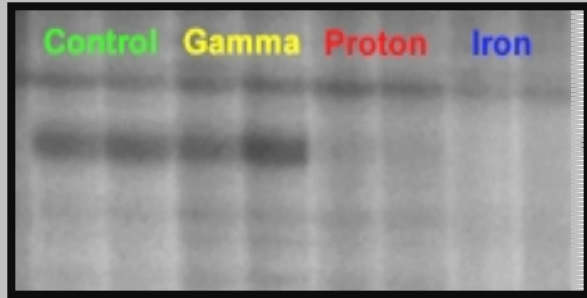
20 Gy gamma at 4 hr post irradiation. 1218 member array.

A. Fornace, Jr. et al.

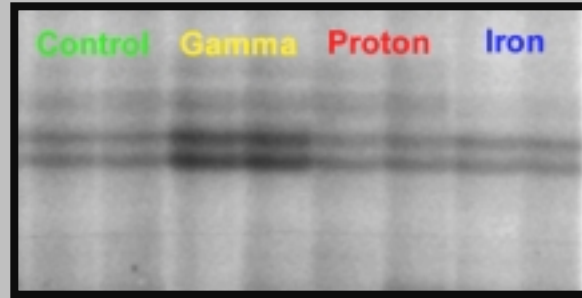


Differential Display Fragment Examples

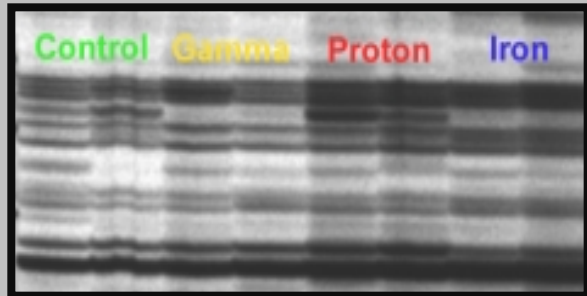
Nematode Gene Expression Levels are Radiation Quality Dependent



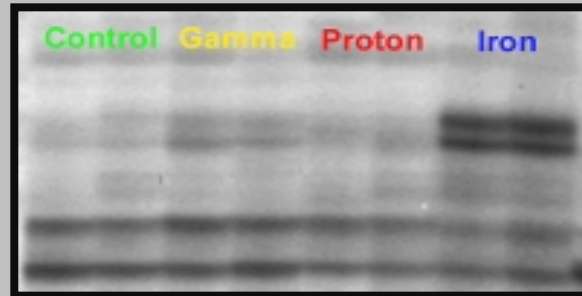
W29-294



W41-282



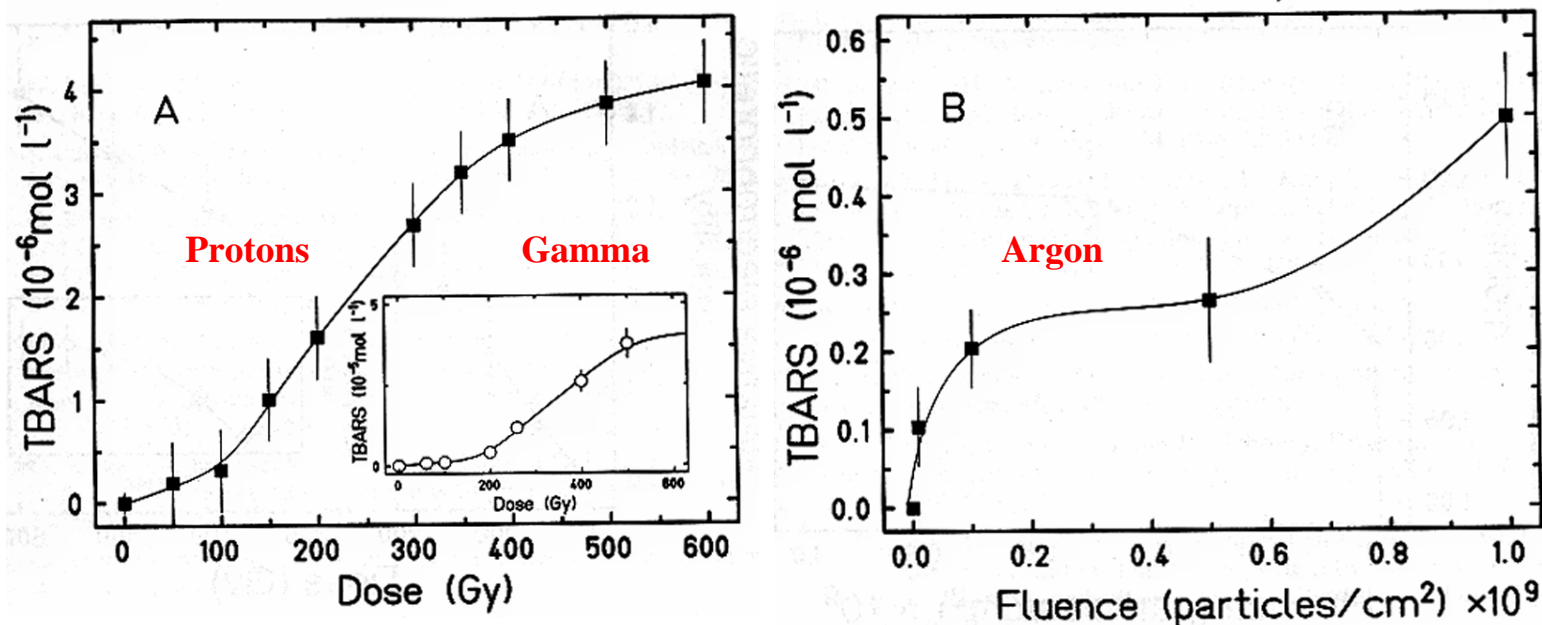
L34-143



L38-272/274

Lipid Damage is LET Sensitive

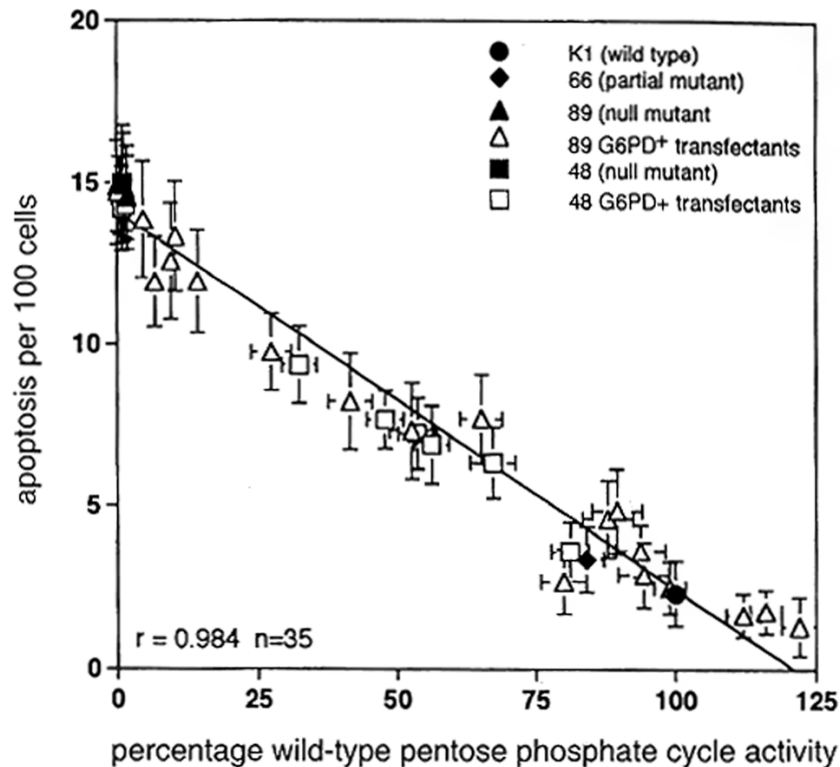
- ◆ Accelerated Protons and Argon Ions Are Highly Effective in Production of Conjugated Dienes.



TBARS (aldehyde-containing thiobarbituric acid acid-reactive substances) were generated from human serum lipids (LDL)

Ordinary Metabolic Activity Levels May Modulate Radiosensitivity

- ◆ The activity of the enzyme G6PD correlates with availability of reducing equivalents as NADH. This in turn modulates oxidative status.



Mutant CHO cells with different G6PD levels were gamma irradiated and scored for apoptosis. Higher G6PD levels were radioprotective.

**Tuttle et al. (2000)
Rad. Res. 153:781.**

Biomarkers

- ◆ Biomarkers are *key events* linking specific environmental exposures to a health outcome via modes of action and detailed molecular mechanisms
- ◆ A *key event* is an empirically observable precursor step that is a necessary element of the mode of action or is a marker for such an element
 - Examples: metabolism, receptor-ligand changes, growth pattern, hormone or physiological perturbations
- ◆ Biomarkers may reflect exposure, effect or susceptibility to an environmental exposure
- ◆ Earlier markers have the greatest potential utility to avert deleterious outcomes while later markers are most closely related to the disease state

Biomarkers

- ◆ Modes of action link key events with sequential processes starting with the interaction of an agent with a cell through functional and anatomical changes and resulting in cancer or other health endpoints.
- ◆ Mechanisms of action are detailed molecular descriptions of the events involved in the induction of cancer or other health endpoints.
- ◆ Susceptibility markers are genetic (eg polymorphisms) or nongenetic such as age, disease state, diet, etc.
- ◆ Exposure markers relate dose to outcome. Microarrays or methods that integrate exposures from multiple pathways are of greatest potential.
- ◆ Effect markers are either early events in direct pathways to disease or predictors of disease/toxicity outside the path but covarying with it.

Conventional vs New Radiobiology

Conventional Principles

- ◆ Cellular target for radiation is DNA in the cell nuclei
- ◆ Cell death is through random denaturation of components and is proportional to DNA double-strand breaks
- ◆ Damage to the genome is dose dependent, occurs immediately, and is passed along to all descendants

New Principles

- ◆ Cell membranes & other structures are also targets
- ◆ Cell death may proceed by controlled disassembly (*apoptosis*)
- ◆ Damage to genome may not be proportional to dose and may not be expressed for up to 50 cell generations (*genomic instability*)

Conventional vs New Radiobiology

Conventional Principles

- ◆ Repair of DNA damage is the critical means of mitigating cell and tissue injury
- ◆ Individual cells autonomously manage damage and survival
- ◆ Effects of exposure to charged particles can be normalized to X-ray effects (*Dose Equivalent Assumption is Valid*)

New Principles

- ◆ Control of signal transduction pathways can mitigate injury and forcing cell death may be more beneficial than promoting survival
- ◆ Injured cells distribute damage to neighbors (*Bystander Effect*)
- ◆ Cells in tissues respond differently than individuals and record their exposure history. (*Microenvironment Effects*)
- ◆ Charged particles produce unique effects so normalization is not valid. (*Dose Equivalent & normalization factors (RBE) are not always valid*)